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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,107	05/23/2005	Charlotta Olsson	1501-1276	5068
<small>465</small> YOUNG & THOMPSON 209 Madison Street Suite 500 ALEXANDRIA, VA 22314			<small>7590</small> EXAMINER CROW, ROBERT THOMAS	
			<small>07/07/2009</small> ART UNIT 1634	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/510,107

Applicant(s)

OLSSON ET AL.

Examiner

Robert T. Crow

Art Unit

1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 15 April 2009.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 19-25, 27-34 and 36-42 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 19-25, 27-34 and 36-42 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SF/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

FINAL ACTION

Status of the Claims

1. This action is in response to papers filed 15 April 2009 in which the specification and claims 19-21, 30, 32-33, 39, and 41 were amended, claims 26 and 35 were canceled, and new claim 42 was added. All of the amendments have been thoroughly reviewed and entered.

The previous rejections under 35 U.S.C. 112, first paragraph, are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 112, second paragraph, not reiterated below are withdrawn in view of the amendments.

The previous rejections under 35 U.S.C. 102(a,e) and 35 U.S.C. 103(a) not reiterated below are withdrawn in view of the amendments. Applicant's arguments have been thoroughly reviewed and are addressed following the rejections necessitated by the amendments.

Claims 19-25, 27-34, and 36-42 are under prosecution.

Claim Objections

2. Claims 27-28 and 36-37 are objected to for the reasons listed below. These objections are new objections necessitated by the amendments.

A. Claims 27 and 36 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the

claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 27 depends on claim 26, which is cancelled. Claim 36 depends upon claim 35, which is cancelled. Thus, neither claim 27 nor claim 36 further limits a previous claim.

B. Claims 28 and 37 are objected to because of the following informalities: claim 28 depends upon claim 27, which depends upon a cancelled claim. Claim 37 depends upon claim 36, which depends upon a cancelled claim. Thus, claims 28 and 37 each depend upon a cancelled claim.

C. Appropriate correction is required.

Specification

4. The amendment filed 15 April 2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. This is a new objection necessitated by the amendments. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Applicant has added the chemical compositions nonyl phenoxypolyethoxyethanol, polysorbate 20, and $C_{14}H_{22}O(C_2H_4O)_n$ with n being an average of 9.5 to the specification based on the original disclosure of the trade names, NP-40, Tween 20, and Triton X-100. However, as noted in the previous Office Action, a trademark or trade name is used to identify a source of goods, and not the goods themselves; thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. Applicant has provided no evidence that the chemical compositions listed in the

amendment were the same chemical compositions known by and sold under the originally filed trade names at the time of filing.

Applicant is required to cancel the new matter in the reply to this Office Action. Alternatively, if Applicant can provide evidence that the amendment is identical in scope to the trade names at the time of filing (e.g., by providing information from a catalog published at the time of filing or other evidence that the trade names and chemicals are in fact the same), the objection will be withdrawn.

It is noted that the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

Claim Rejections - 35 USC § 112, First Paragraph

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 32 and 41 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This is a new matter rejection necessitated by the amendments. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has added the chemical compositions "nonyl phenoxy-polyethoxy-ethanol," "polysorbate 20," and "C₁₄H₂₂O(C₂H₄O)_n with n being an average of 9.5" to

claims 32 and 41 based on the original disclosure of the trade names, NP-40, Tween 20, and Triton X-100. However, as noted in the previous Office Action, a trademark or trade name is used to identify a source of goods, and not the goods themselves; thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name. Applicant has provided no evidence that the chemical compositions listed in the amendment were the same chemical compositions known by and sold under the originally filed trade names at the time of filing. Thus, the recitations "nonyl phenoxypolyethoxy-ethanol," "polysorbate 20," and " $C_{14}H_{22}O(C_2H_4O)_n$ with n being an average of 9.5" constitute new matter.

As noted above, if Applicant can provide evidence that the amendment is identical in scope to the trade names at the time of filing (e.g., by providing information from a catalog published at the time of filing or other evidence that the trade names and chemicals are in fact the same), the rejection will be withdrawn.

It is noted that the Response above should not be construed as an invitation to file an after final declaration.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 27-28, 33-34, and 36-41 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. This is a new rejection necessitated by the amendments.

Claims 27 and 36, upon which claims 28 and 37 respectively depend, each depend upon a cancelled claim. Thus, the dependency of claims 27 and 36 is unclear.

For the purposes of examination, claim 27 is interpreted as being dependent upon claim 19, and claim 36 is interpreted as being dependent upon claim 33.

B. This rejection is maintained from the previous Office Action.

Claims 33-34, and 36-41 are indefinite in claim 33, which recites the limitation "extending the primer by reading the result of the primer extension" in lines 7-8 of claim 33. The recitation "extending the primer by reading the result of the primer extension" is indefinite because it is unclear how "reading the result" of the primer extension results in "extending the primer" (i.e., extending the primer "by" reading the result). In addition, the recitation of "the primer extension" lacks antecedent basis because the claims do not previously recite a primer extension. It is suggested that the claims be amended to clarify the relationship between reading the result and extending the primer.

Response to Arguments

Applicant's arguments filed 15 April 2009 (hereafter the "Remarks") have been fully considered but they are not persuasive for the reason(s) discussed below.

Applicant argues on page 12 of the Remarks that the amendments have overcome the previous rejection of the claims under 35 USC 112, second paragraph.

However, as noted in the previous Office Action, the indefinite limitation "extending the primer by reading the result of the primer extension" is also present lines

7-8 of claim 33. Applicant has not amended claim 33. Therefore, the rejection is maintained from the previous Office Action.

9. The following rejections are new rejections necessitated by the amendments.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 19-25, 29, 31, 33-34, 38, 40, and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990).

Regarding claims 19 and 29, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 19) and the linker is shorter than 8 atoms (i.e., claim 29).

However, Urdea et al teach functionally equivalent labeled cleavable nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 19; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH₂ linker, and NH connects to the base (i.e., claim 29; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of cleavable labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the labeled cleavable nucleotides are the functionally equivalent labeled cleavable nucleotides having a cleavable linker that is a disulfide linker (i.e., claim 19) that is less than 8 atoms (i.e., claim 29) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have

resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

Regarding claims 20-21, the method of claim 19 is discussed above. Quake et al teach the amount of labeled derivative of the at least one nucleotide in said mixture is 19% (i.e., less than 20%; paragraph 0179), which is within the range of 5-50 mole % (i.e., claim 20) and also within the range of 10-50 mole % (i.e., claim 21).

Regarding claim 22, the method of claim 19 is discussed above. Quake et al also teach the single stranded form of said nucleic acid molecule is attached to a carrier; namely, the single stranded polynucleotide template is immobilized to the surface of a channel (paragraph 0055).

Regarding claim 23, the method of claim 22 is discussed above. Quake et al further teach the mechanism of attachment to the carrier is specific binding to biotin (paragraph 0057).

Regarding claim 24, the method of claim 23 is discussed above. Quake et al teach the carrier is a surface; namely, the surface of a channel (paragraph 0055).

Regarding claim 25, the method of claim 19 is discussed above. Quake et al also teach the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 31, the method of claim 19 is discussed above. Quake et al further teach the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Regarding claims 33 and 38, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186) or by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach

a cleavable link between the label and the nucleotide that is a disulfide (i.e., claim 33) and the linker is shorter than 8 atoms (i.e., claim 38).

However, Urdea et al teach functionally equivalent detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (i.e., claim 33; column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH₂ linker, and NH connects to the base (i.e., claim 38; column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled nucleotides attached with a cleavable linker as taught by Quake et al so that the cleavable labeled nucleotides are the functionally equivalent cleavable labeled nucleotides comprising a cleavable linker in the form of a disulfide linker (i.e., claim 33) that is less than 8 atoms (i.e., claim 38) as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly

taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

Regarding claim 34, the method of claim 33 is discussed above. Quake et al teach the label is neutralized by photobleaching (paragraph 0193).

Regarding claim 40, the method of claim 33 is discussed above. Quake et al also teach the derivative of the nucleotide is a dideoxynucleotide (paragraph 0185).

Regarding claim 42, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines

the identity of the incorporated nucleotide (paragraph 0014). The label is then removed by photobleaching (paragraph 0193), and the removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

It is noted that the claim requires either neutralizing the label or cleaving the cleavable link. Thus, the limitations regarding "the cleavage" (i.e., adding a reducing agent, exposing a thiol group, capping the thiol group) are not required when the method performs the neutralization procedure rather than the cleavage procedure.

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide and the linker is shorter than 8 atoms.

However, Urdea et al teach functionally equivalent detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH₂ linker, and NH connects to the base (column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of cleavable labeled nucleotides attached with a cleavable linker as taught by Quake et al so are functionally equivalent cleavable labeled nucleotides comprising the cleavable linker that is a disulfide linker that is less than 8 atoms as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides comprising the cleavable disulfide linker of Urdea et al predictably results in a link useful in the labeling of nucleotides.

13. Claims 27-28 and 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Wells et al (J. Biol. Chem., vol. 261, pages 6564-6570 (1986)).

Regarding claims 27-28 and 36-37, the methods of claims 19 and 33 are discussed above in Section 12.

Neither Quake et al nor Urdea teach cleavage is performed by addition of a reducing agent to expose and provide a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

However, Wells et al teach the disulfides are cleaved with reducing agents to yield free thiol, which are capped by reaction with iodoacetamide to prevent reformation of disulfides (page 6566, column 1, last paragraph). Thus, Wells et al teach the known technique of reductively cleaving a disulfide to form a thiol group (i.e., claims 27 and 36) that is capped by a reagent (i.e., claims 28 and 37).

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of disulfide linked labeled nucleotides as taught by Quake et al in view of Urdea et al so that the link is reductively cleaved to generate a thiol (i.e., claims 27 and 36) that is capped with a reagent (i.e., claims 28 and 37) as taught by Wells et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing the reformation of the disulfides after cleavage as explicitly taught by Wells et al (page 6566, column 1, last paragraph). In addition, it would have been obvious to the ordinary artisan that the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al could have been applied to the method of Quake

et al in view of Urdea with predictable results because the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al predictably results in prevention of the reformation of the disulfide link after cleavage.

14. Claims 30 and 39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Uemori et al (PCT International Application Publication No. WO 97/24444, published 10 July 1997), as evidenced by Atkins (Physical Chemistry, 3rd Ed., Freeman and Co., New York, 1986, page 278). Citations from Uemori et al are from the National Stage (U.S. Patent No. 6,395,526 B1, issued 28 May 2002). The National Stage is deemed an English language translation of the PCT.

Regarding claims 30 and 39, the methods of claims 19 and 33 are discussed above in Section 12.

Quake et al teach the cleavage of the linker in step c) is done with mild acid (paragraph 0186). Acidic conditions result in a pH of less than 7, as evidenced by Atkins (page 278). Thus, while Quake et al teach the cleavage portion of step c) is done at a pH below 7, Quake et al does not teach the extension with polymerase occurs at a pH below 7.

However, Uemori et al teach extension reactions of primer template/complexes using a DNA polymerase (Abstract) wherein the polymerase exhibits maximum activity at a pH of 6.5 (column 12, lines 13-16). Uemori et al also teach the DNA polymerase having the activity at pH 6.5 has the added advantage of higher primer extensibility (Abstract) with a lower error rate in DNA synthesis (column 13, lines 30-35), which improves the assay accuracy. Thus, Uemori et al teach the known technique of performing primer extension at a pH below 7.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of a DNA polymerase and cleavage of a linker at a pH below 7 as taught by Quake et al to use the DNA polymerase of Uemori et al to arrive at the instantly claimed method with a reasonable expectation of success. Use of the polymerase of Uemori et al would result in extension reactions performed at a pH 6.5. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method providing the maximum activity of the polymerase and the added advantage of higher primer extensibility with improved assay accuracy as a result of the lower error rate in DNA synthesis of the polymerase as explicitly taught by Uemori et al (Abstract and column 13, lines 30-35). In addition, it would have been obvious to the ordinary artisan that the known technique of using the pH of Uemori et al could have been applied in step c) of the method of Quake et al in with predictable results because the known technique of using the pH of Uemori et al predictably results in a viable primer extension reaction.

15. Claims 32 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) as applied to claims 19 and 33 above, and further in view of Hyman (U.S. Patent No. 5,516,664, issued 14 May 1996).

Regarding claims 32 and 41, the methods of claims 19 and 33 are discussed above in Section 12.

While Quake et al teach a label that is cleaved (paragraph 0186), Quake et al do not teach a functionally equivalent label is cleaved using an agent in the form of alkaline phosphatase.

However, Hyman teaches the extension of a primer using a functionally equivalent blocked nucleotide, wherein the blocking group is removed with an agent in the form of a phosphatase (Abstract); namely, alkaline phosphatase (Example 5). Thus, Hyman teaches the known technique of extending a nucleic acid with a label that is removed using an agent in the form of alkaline phosphatase.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method of Quake et al so that the blocking label is the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman to arrive at the instantly claimed method with a reasonable expectation of success. It would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent label that

is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman could have been applied as the label in the method of Quake et al in with predictable results because the known technique of using the functionally equivalent label that is cleaved using an agent in the form of alkaline phosphatase as taught by Hyman predictably results in a functionally equivalent label for blocking a primer extension reaction.

16. Claim 42 is rejected under 35 U.S.C. 103(a) as being unpatentable over Quake et al (U.S. Patent Application Publication No. US 2002/0025529 A1, published 28 February 2002, originally filed on 6 November 2000 as U.S. Application No. 09/707,737) in view of Urdea et al (U.S. Patent No. 4,910,300, issued 20 March 1990) in view of Wells et al (J. Biol. Chem., vol. 261, pages 6564-6570 (1986)).

It is noted that while claim 42 has been rejected under 35 U.S.C 103(a) as described above in Section 12, the claim is also obvious using the interpretation outlined below.

Regarding claim 42, Quake et al teach a method comprising providing a single stranded polynucleotide template (i.e., nucleic acid molecule) to which a primer is hybridized (paragraphs 0055 and 0146), thus forming a template/primer complex. A polymerase and one of the four nucleotide triphosphates are then added (paragraph 0055). The nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. The unlabeled nucleotide is the claimed at least one nucleotide, and the labeled nucleotide is the

claimed at least one labeled derivative of the at least one nucleotide. The label is attached with a cleavable link (paragraph 0186). The primer is extended via the extension reaction and the result is read; namely, the signal from the label determines the identity of the incorporated nucleotide (paragraph 0014). The label is then removed either by cleaving the cleavable link (paragraph 0186). The removal is prior to the next extension cycle (paragraph 0216). The extension step and reading step is then repeated with the next nucleotide mixture (paragraph 0014).

While Quake et al teach the labels are fluorescent labels and that the labels are cleaved via a cleavable linker arm (paragraph 0186), Quake et al do not explicitly teach a cleavable link between the label and the nucleotide that is a disulfide and the linker is shorter than 8 atoms.

However, Urdea et al teach detectably labeled nucleotides (column 8, lines 20-60), wherein the detectable label is a fluorescent label (column 4, lines 5-10) and is linked to the nucleotide with a cleavable linker in the form of a disulfide linker (column 8, lines 20-60). The linker between the disulfide bridge and the base is less than 8 atoms; namely, Formula 13 has label R1, a disulfide for R2, x is one CH₂ linker, and NH connects to the base (column 8, lines 20-60). Urdea et al further teach that the nucleotides having the linkers and labels have the added advantage of being inexpensively synthesized in large quantity (column 2, lines 15-40). Thus, Urdea et al teach the known technique of using a disulfide as a cleavable link between a label and a nucleotide.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of labeled cleavable nucleotides attached with a cleavable linker as taught by Quake et al so that the labeled cleavable nucleotides are the functionally equivalent labeled cleavable nucleotides comprising a cleavable linker that is a disulfide linker that is less than 8 atoms as taught by Urdea et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of having a decreased cost as a result of utilizing labels that are inexpensively synthesized in large quantity as explicitly taught by Urdea et al (column 2, lines 15-40). In addition, it would have been obvious to the ordinary artisan that the known technique of using the functionally equivalent labeled cleavable nucleotides of Urdea et al could have been applied as the labeled cleavable nucleotides in the method of Quake et al with predictable results because the known technique of using the functionally equivalent labeled cleavable nucleotides of Urdea et al predictably results in a link useful in the labeling of nucleotides.

While Quake et al teach the label is then removed by cleaving the cleavable link (paragraph 0186), neither Quake et al nor Urdea teach cleavage is performed by addition of a reducing agent to expose and provide a thiol group that is capped by a reagent.

However, Wells et al teach the disulfides are cleaved with reducing agents to yield free thiol, which are capped by reaction with iodoacetamide to prevent reformation

of disulfides (page 6566, column 1, last paragraph). Thus, Wells et al teach the known technique of reductively cleaving a disulfide to form a thiol group that is capped by a reagent.

It would therefore have been obvious to a person of ordinary skill in the art at the time the claimed invention was made to have modified the method comprising the use of disulfide linked labeled nucleotides as taught by Quake et al in view of Urdea et al so that the link is reductively cleaved to generate a thiol that is capped with a reagent as taught by Wells et al to arrive at the instantly claimed method with a reasonable expectation of success. The ordinary artisan would have been motivated to make the modification because said modification would have resulted in a method having the added advantage of preventing the reformation of the disulfides after cleavage as explicitly taught by Wells et al (page 6566, column 1, last paragraph). In addition, it would have been obvious to the ordinary artisan that the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al could have been applied to the method of Quake et al in view of Urdea with predictable results because the known technique of forming and capping an exposed thiol via reduction of a disulfide as taught by Wells et al predictably results in prevention of the reformation of the disulfide link after cleavage.

Response to Arguments

A. Applicant argues on page 13 of the Remarks that the amendments overcome the anticipation of the claims by Quake et al. These arguments have been

considered but are moot in view of the new ground(s) of rejection necessitated by the amendments.

B. Applicant argues on page 13 of the Remarks that the present invention requires labeled derivatives having a fluorophore linked to the nucleotide via a cleavable link having a disulfide bond, and further argues on page 14 of the Remarks that Quake et al do not teach these nucleotides.

However, as noted in the previous Office Action and presented in the new rejections above, Urdea et al teach functionally equivalent cleavable labeled derivatives having a fluorophore linked to the nucleotide via a cleavable link having a disulfide bond. Thus, the substitution of the functionally equivalent labeled cleavable nucleotide derivatives of Urdea et al for the labeled cleavable nucleotide derivatives of Quake et al is obvious for the reasons stated above.

C. Applicant argues on page 15 of the Remarks that the present invention is not restricted to the use of a microfabricated synthesis channel.

However, any additional limitations are encompassed by the open claim language "comprising" in the instant claims.

In addition, while claim 1 of Quake et al requires a synthesis channel, claim 1 of Quake is not a limiting embodiment Quake et al.

Further, it is noted that the features upon which Applicant's argument relies (i.e., performance of the method without a synthesis channel) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from

the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

D. Applicant argues on page 15 of the Remarks that neither Quake nor Urdea et al disclose the amount of labeled derivative is in the range of 1-50 mole %.

However, as noted in the rejections above, Quake et al teach the nucleotides in the extension reaction a mixture of labeled and unlabeled nucleotides, wherein the percentage of labeled nucleotides is 19% (i.e., less than 20%; paragraph 0179), which is within the claimed range of 1-50 mole %. Thus, Applicant's argument is totally incorrect.

E. Applicant argues on page 15 of the Remarks that the other prior art references fail to correct the alleged deficiencies of Quake et al in view of Urdea et al. However, since the arguments regarding the alleged deficiencies of Quake et al in view of Urdea et al were not persuasive for the reasons presented above, the claims remain rejected for the reasons presented above.

F. Applicant argues on pages 15-18 of the Remarks that the claimed invention displays unexpected results, as presented in Figures 5-8.

However, the data presented in Figures 5-8 is based on the experimental procedure detailed in Example 4, and does not show any comparison to other methods (e.g., the method of Quake et al) so as to establish the alleged unexpected superior results. In fact, page 32 of the instant specification states that Figures 5-8 "show the selectivity of the polymerase for labeled against non-labeled nucleotides (emphasis added by the examiner)." Thus, the data does not show any advantage of using the

claimed labeled nucleotides over any other labeled nucleotides (e.g., those of Quake et al). Thus, Applicant has resented no evidence that the claimed labeled nucleotides offer unexpected results over the labeled nucleotides of Quake et al

It is noted that the Response above should not be construed as an invitation to file an after final declaration. See MPEP 715.09 [R-3].

In addition, the data presented in Figures 5-8 (based on the experimental procedure detailed in Example 4 of the instant specification) is not commensurate in scope with the instant claims for the following reasons:

- i. The data is limited to specific biotinylated, fluorescein labeled oligonucleotides immobilized on streptavidinated beads; neither the specific oligonucleotides, biotin, fluorescein, nor streptavidinated beads are required by the instant claims.
- ii. The data is limited to specific buffers, temperatures, volumes and concentrations of reagents, as well as specific reaction steps (e.g., washing with TENT buffer); none of these limitations are required by the instant claims.
- iii. The data is limited to Cy5-SS-dNTPs, whereas the claim encompasses any labeled nucleotide having a fluorophore and a disulfide bond.
- iv. The data is limited to Klenow exo- polymerase, whereas the claim encompasses the use of any polymerase.
- v. The data is based on a pyrosequencing step not required by the instant claims.

Therefore, the method having the alleged unexpected results is not

commensurate in scope with the instant claims, and the claims remain rejected as obvious over the prior art for the reasons cited above. See MPEP 716.02(d)[R-2].

Conclusion

17. No claim is allowed.
18. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).
19. A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.
20. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert T. Crow whose telephone number is (571)272-1113. The examiner can normally be reached on Monday through Friday from 8:00 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/R. T. C./
Examiner, Art Unit 1634

Robert T. Crow
Examiner
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/JD Schultz/

Supervisory Patent Examiner, Art Unit 1635